UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: **November 20, 2018**

SUBJECT: **Revised Oxytetracycline/Oxytetracycline Hydrochloride/Oxytetracycline Calcium:** Draft Human Health Risk Assessment in Support of Registration Review and Tolerance Establishment in/on Citrus Fruit Crop Group 10-10.

PC Code: 006304, 006321 (Calcium), and 006308 (HCl)
Decision No.: 510568 & 545307
Petition No.: 5F8415

Risk Assessment Type: Single Chemical/Aggregate
TXR No.: NA

MRID No.: NA

DP Barcode: D449380 and D449423

Registration No.: 71185-5 and 80990-1
Regulatory Action: Section 3 Registration & Registration Review
Case No.: 0655
CAS No.: 79-57-2, 7179-50-2 (Calcium) and 2058-46-0 (HCl)
40 CFR: §180.337

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The Registration Division (RD) and Pesticide Re-Evaluation Division (PRD) have requested that the Health Effects Division (HED) conduct a Human Health Risk Assessment to support tolerance establishment for use on citrus fruit (CG 10-10) and registration review, respectively. This version supersedes the previous Risk Assessment dated 11/1/2016.

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1.0 Executive Summary

This assessment has been conducted to address the requirement for a Draft Risk Assessment (DRA) to support registration review and the Section 3 proposed tolerance petition for a new use in/on citrus fruit (CG 10-10). As part of registration review and the tolerance petition, the Pesticide Re-Evaluation Division (PRD) and Registration Division (RD), of the Office of Pesticide Programs (OPP), respectively, have requested that the Health Effects Division (HED) evaluate the available hazard, residue chemistry, and exposure data for oxytetracycline. This evaluation will be used to conduct dietary and occupational/residential assessments, as needed, to estimate the risk to human health that will result from the currently registered and proposed uses of oxytetracycline. Geo Logic Corporation has requested the registration of AgroSource Oxytetracycline Technical Fungicide/Bactericide Agricultural Oxytetracycline (Reg. No. 71185-5) and FireLine 17 WP (EPA Reg. No. 80990-1) and the establishment of tolerances in/on citrus fruit (CG 10-10).

Background

Oxytetracycline (PC Code 006304), part of the tetracycline class, is a broad-spectrum antibiotic produced from the actinomycete *Streptomyces rimosus*. Two salts of oxytetracycline, hydroxytetracycline monohydrochloride (oxytetracycline hydrochloride) (PC Code 006308) and oxytetracycline calcium (PC Code 006321), are the forms of oxytetracycline registered as pesticides for preventing the growth or killing bacteria, fungi and mycoplasma-like organisms; there are no active registrations for PC Code 006304. The toxicity of all three forms of oxytetracycline would be expected to be similar and are considered equivalent.

Humans may be exposed to oxytetracycline in food and drinking water. Oxytetracycline may be applied directly to growing crops and application may result in oxytetracycline reaching surface and ground sources of drinking water. There are no residential uses of oxytetracycline as a pesticide; therefore, residential handler and post-application pesticidal exposures that might result from such uses are not expected. There are uses that could result in spray drift, leading to the potential for non-occupational dermal and incidental oral exposures. Occupational uses could result in dermal and inhalation occupational handler and post-application exposures. A dermal assessment was not conducted for non-occupational or occupational handler exposure because of the low potential for dermal absorption of oxytetracycline (See Section 4.2.1).

Tolerances are established in the 40 CFR §180.337 for residues of oxytetracycline in/on apple, pear and peach at 0.35 ppm. Oxytetracycline is also approved by the Food and Drug Administration (FDA) for use as a human and animal drug to treat a variety of bacterial infections. In conjunction with the FDA-approved animal drug uses, food-additive tolerances up to 12 ppm are established for residues of tetracyclines in commodities of beef cattle, dairy cattle, calves, swine, sheep, chickens, turkeys, finfish, and lobster in tissues and milk (21 CFR §556.500).

Previous to this risk assessment, the next most recent human health risk assessment for oxytetracycline was to support a Section 18 Emergency Exemption request for use of FireLine 17 WP (EPA Reg. No. 80990-1) and Mycoshield® (EPA Reg. No. 55146-97) on citrus to control *Candidatus liberibacter asiaticus* (CLas) bacterium, the cause of citrus greening disease

(Negrón-Encarnación, 02/29/2016, D430825).
Since the previous assessment, the following risk assessment updates have been made:

- Based on a review of the hazard database and all available tetracycline toxicity data, the uncertainty factor for chronic dietary exposures has been revised to 1000X. Additionally, a short- and intermediate-term occupational inhalation point of departure (POD) has been selected, when previously no PODs were selected.
- The chronic dietary exposure assessment has been reevaluated to incorporate the proposed uses of oxytetracycline, updated policies, and the revised uncertainty factor.
- A quantitative non-occupational spray drift exposure/risk assessment was completed.
- An occupational handler exposure assessment has been conducted to evaluate inhalation exposures from the registered and proposed uses of oxytetracycline.

Hazard Assessment

As part of the registration review evaluation for oxytetracycline, HED has concluded that additional toxicity data are not required because the available laboratory animal toxicity data, in conjunction with the conclusions that can be drawn from the decades of use of oxytetracycline as a human antibiotic drug without significant incidents, is sufficient to assess the safety of oxytetracycline; therefore, additional toxicity data have been waived by the agency.

Oxytetracycline has been prescribed to patients older than 8 years old and non-pregnant women for many decades, typically at doses 1000 -2000 mg/day. At these high doses, no significant incidents were reported in adults other than those typically associated with antibiotic use such as gastrointestinal reactions and possibly rare photosensitive reactions. Therefore, the absence of a pattern of significant incidents associated with the historical use of the drug in adults and the assumption that any potential systemic hazard related to oxytetracycline exposure would have been well-characterized if such hazard was occurring, led HED to conclude that no additional systemic toxicity data are required to assess the safety of oxytetracycline for these populations.

Tetracyclines exert their activity in bacteria by inhibiting protein synthesis. At high doses the target organ of tetracycline toxicity is the liver. The most common effect in intermediate- or long-term oral exposures in rats and mice was a decrease in body weight. In the prenatal developmental study in rats clinical signs included increased incidences of respiratory signs and rough hair coat in the dams, in addition to increased mortality and a decreased percentage of dams found pregnant. Also identified was a decrease in fetal body weight. In the mouse prenatal developmental study, there was no toxicity identified in the dams or fetuses. In all of the above animal studies, adverse effects were seen at doses that exceed the limit dose. There is no adequate reproductive toxicity study available in the database, however, the data requirement was waived based on the lack of reproductive effects reported during the history of use as a drug. No evidence of neurotoxicity was observed in any guideline study. A rat immunotoxicity study demonstrated immunosuppression at doses lower than those for systemic toxicity. Tetracyclines are known to inhibit bone growth in developing tissue. When oxytetracycline was administered orally as a single dose to two female infant rhesus monkeys, zygomatic arch bone (lateral surface of temporal bone) growth was inhibited for ~12.5 days with no recovery observed by 21 days. Bone developmental effects were also observed after administration of chlortetracycline and

demethylchlortetracycline in adult rhesus monkeys highlighting the consistency of tetracycline treatment across this class of chemicals.

Based on the results of the monkey study which measured bone developmental effects in young monkeys, HED is adding appropriate safety factors to assure that risks to children and developing fetuses would not be underestimated. Based on doses at which effects were seen in this monkey study compared to the significantly lower exposures expected from use of oxytetracycline when used as a pesticide and the application of safety factors to derive a point of departure using the available toxicity data, the Agency concludes for that there is no need for additional toxicity data to assess the safety of oxytetracycline for pregnant women, developing fetuses, and children 8 years old and younger.

Oxytetracycline was classified as a "Group D: Not Classifiable as to Human Carcinogenicity". Oxytetracycline has a low acute toxicity, being Toxicity Category IV for oral toxicity, the only acute lethality study available in the database.

Endpoints and Uncertainty Factors for Risk Assessment

The chronic dietary, incidental oral, and inhalation endpoints were established based on a weight-of-evidence (WOE) approach from five chronic studies; three chronic rat studies and two chronic dog studies. In the rat chronic toxicity/carcinogenicity study, effects observed included fatty metamorphosis and an increase in accessory structures of the liver seen at the lowest observed adverse effect level (LOAEL) of 1250 mg/kg/day; the lowest dose tested (LDT). In two additional chronic rat studies, no adverse effects were observed up to the highest dose tested (HDT) (50 and 150 mg/kg/day). In the chronic dog studies, no adverse effects were seen at the HDT (250 mg/kg/day). Based on a WOE approach from the five chronic studies, a NOAEL of 100 mg/kg/day has been selected as the point of departure for chronic dietary, incidental oral and inhalation endpoints. No specific LOAEL has been established.

Based on the adverse effects seen in infant rhesus monkeys after oral administration of oxytetracycline and the lack of a NOAEL, the Food Quality Protection Act (FQPA) Safety Factor (SF) will be retained at 10X (See Section 4.4). HED recommends the inclusion of the 100X uncertainty factor (UF) for both interspecies and intraspecies variability. Therefore, a level of concern (LOC) of 1000 is applicable for all sub-populations' routes of exposure, and durations of exposure.

A dermal assessment was not conducted for non-occupational or occupational handler exposure because of the low potential for dermal absorption of oxytetracycline (See Section 4.2.1). An acute dietary endpoint was not evaluated because no appropriate endpoint for females age 13-49 or for the general population attributable to a single exposure was identified.

Residue Chemistry and Dietary (Food and Water) Exposure and Risk

The residue chemistry database is complete for oxytetracycline and adequate field trial data have been provided to support the proposed new use on citrus fruit crop group 10-10. The residue of concern for tolerance and risk assessment purposes is parent compound oxytetracycline.

An acute dietary assessment was not conducted, since no appropriate endpoint attributable to a single exposure was identified in the toxicity database. Oxytetracycline was classified as "Not Classifiable as to Human Carcinogenicity"; therefore, a cancer dietary assessment has not been completed. An unrefined chronic dietary (food and drinking water) exposure and risk analysis was conducted using tolerance-level residues for all the registered and proposed crops; 100% crop treated (CT) assumptions; default processing factors (PFs) for all processed commodities except citrus juice, citrus oil, and citrus peel, since concentration is not expected (i.e., empirical PFs <1X); and tolerances established for livestock and fish commodities resulting from uses as an animal drug. Model-derived estimated drinking water concentrations (EDWCs) for all direct and indirect water sources were provided by the Environmental Fate and Effects Division (EFED) for these analyses. The estimated exposure (food and drinking water) from the existing and proposed new uses of oxytetracycline resulted in an estimated risk equivalent to 11% of the chronic population adjusted dose (cPAD) for the general U.S. population. The most highly exposed population subgroup was children 1-2 years old with an estimated exposure equivalent to 33% of the cPAD.

Residential (Non-Occupational) Exposure and Risk

There are no proposed or registered residential pesticide uses of oxytetracycline; therefore, a quantitative residential assessment has not been performed.

Non-Occupational Spray Drift/Volatilization/Residential Bystander Exposure and Risk

A quantitative non-occupational incidental oral spray drift assessment was conducted for children (1<2 years). Incidental oral risk estimates from indirect exposure to oxytetracycline related to spray drift are not of concern at the field edge (LOC = 1000); and MOEs range from 93,000 to 170,000. Non-occupational dermal exposure resulting from spray drift onto residential areas was not assessed because a dermal POD was not selected.

Aggregate Risk

There are no registered residential pesticide uses of oxytetracycline; therefore, the aggregate risk assessment includes only background (chronic) dietary exposures from food and drinking water. There are no dietary or aggregate risks of concern for the existing and proposed uses of oxytetracycline.

Pharmaceutical Aggregate Risk

Tetracycline hydrochloride (97% chemical similarity to oxytetracycline; TOXNET) is approved by the FDA for use as an oral antibiotic to treat certain bacterial and parasitic infections. Relative to the FDA-approved tolerances and therapeutic doses, however, the exposure to pesticide residues of oxytetracycline on treated agricultural commodities and drinking water containing oxytetracycline is low. Because the pesticide exposure has no more than a minimal impact on the total dose to a pharmaceutical user, EPA concludes that there is a reasonable

certainty that the potential dietary pesticide exposure will result in no harm to a user being treated therapeutically with oxytetracycline.

Occupational Exposure and Risk

The occupational handler exposure and risk estimates indicate that the short- and intermediate-term inhalation MOEs are not of concern to HED (i.e., MOEs ≥ 1000) with baseline attire (i.e., no gloves and no respirator). The MOEs range from 380,000 to 83,000,000.

Occupational post-application dermal exposure was not quantitatively assessed because of the low dermal absorption that is expected based on the chemical properties of the compound and a dermal POD was not selected. Based on the Agency's current practices, a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed for oxytetracycline at this time.

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (https://www.epa.gov/laws-regulations/summary-executive-order-12898-federal-actions-address-environmental-justice).

2.0 HED Conclusions and Recommendations

2.1 Data Deficiencies

HED has examined the toxicology, residue chemistry and exposure databases for oxytetracycline and has determined there are no data deficiencies.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

Adequate enforcement methods are available for determining oxytetracycline residues in/on plant commodities.

For tolerance enforcement on apple, pear, and peach, Method STM2028.06 is considered scientifically acceptable. Briefly, homogenized fruit samples (5 grams) are extracted by shaking with a solution of 10 mM ethylenediaminetetraacetic acid (EDTA) in a solvent of 50 mM ammonium acetate (pH 4): methanol (90:10, v:v). After centrifugation, an internal standard (demeclocycline) is added to the extract, and it is analyzed with LC/MS/MS using turbo ion spray in the positive ion mode. The limit of quantitation (LOQ, determined as the lowest level of method validation; LLMV) is 0.10 ppm. The method monitors two ion transitions: *m/z*

461→426 for quantitation, and *m/z* 461→443 for confirmation of oxytetracycline. No additional confirmatory procedures are needed. The method was adequately validated for the quantitation and confirmation ion transitions using samples of apple and nectarine. A successful independent laboratory validation (ILV) was performed using samples of apple, pear, peach, and nectarine. During the ILV, a typographical error was identified in the method for the fortification standard preparation for oxytetracycline hemicalcium. It was determined that the changes made/identified during the ILV must be incorporated into the method.

To support this requested new use of oxytetracycline on citrus fruit crop group 10-10, the registrant has proposed a high performance liquid chromatography method with tandem mass spectrometry detection (LC/MS/MS) for tolerance enforcement. This method, "The Analytical Method for the Analysis of Oxytetracycline Residues in Citrus," performs sample extraction using 1% acetic acid. For some citrus processed commodities, 0.1% formic acid is required in the extraction sequence. Following extraction, samples are then filtered and analyzed by LC/MS/MS analysis. For the determination of oxytetracycline, the method monitors the ion transitions of *m/z* 461.2 → 426.1 for quantitation and *m/z* 461.2 → 443.1 for confirmation. The LOQ is 0.01 ppm for all citrus matrices determined as the LLMV. The estimated limit of detection (LOD) is reported to be 0.002 ppm.

Conclusions: The proposed tolerance enforcement method for citrus fruit was used for data collection in the supporting field trial studies and adequate validation results were provided in the submission. A successful ILV study was also provided in the submission. Given these data and the fact that a confirmatory ion transition is also monitored, the Agency concludes that this LC/MS/MS method developed by the registrant is acceptable for oxytetracycline tolerance enforcement on citrus commodities.

2.2.2 Recommended Tolerances

HED has examined the residue chemistry database for oxytetracycline. There are no residue chemistry issues that would preclude the establishment of the requested oxytetracycline citrus fruit tolerance. Table 2.2.2 summarizes HED's recommendations for establishing this tolerance. The current tolerance expression for oxytetracycline [40 CFR §180.337(a)] is consistent with HED's Interim Guidance on Tolerance Expressions (S. Knizner, 05/27/2009) and appropriately reads as follows:

> "Tolerances are established for residues of the fungicide/bactericide oxytetracycline, including its metabolites and degradates, in or on the commodities in the table in this paragraph. Compliance with the tolerance levels specified in this paragraph is to be determined by measuring only oxytetracycline, (4S,4aR,5S,5aR,6S,12aS)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide, in or on the commodity."

Table 2.2.2. Tolerance Summary for Oxytetracycline, §180.337(a).

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
Fruit, citrus, group 10-10	0.01	0.01	NA

2.2.3 Revisions to Petitioned-For Tolerances

There are no revisions needed to the proposed tolerance. The use of the LOQ for citrus crops was used for tolerance derivation because residues in the field trials were not measurable. The recommended tolerance matches the limit proposed by the registrant.

2.2.4 International Harmonization

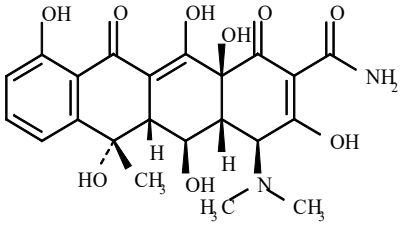
There are no Codex, Canadian, or Mexican established maximum residue limits (MRLs) for residues of oxytetracycline (personal communication, M. Negussie, 07/07/2016). As a result, there are no international harmonization issues and none are expected to arise from establishment of the recommended new tolerance on citrus fruit crop group 10-10.

A spreadsheet summarizing the U.S. and international residue limits established for oxytetracycline is presented in Appendix B.

3.0 Introduction

3.1 Chemical Identity

Table 3.1. Nomenclature of Oxytetracycline

Chemical Structure	
Empirical Formula	$C_{22}H_{24}N_2O_9$
Common Name	Oxytetracycline
Molecular Weight	496.47
IUPAC name	(4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-4-dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxonaphthacene-2-carboxamide
CAS Name	(4S,4aR,5S,5aR,6S,12aS)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide
CAS Registry Number	79-57-2
End-use product/EP	See Table 3.3
Chemical Class	Tetracycline

3.2 Physical/Chemical Characteristics

A table with the physicochemical characteristics of oxytetracycline hydrochloride and oxytetracycline calcium is included in Appendix C.

Oxytetracycline is an odorless beige tinted powder. Oxytetracycline is considered moderately soluble in surface and groundwater, but its exact solubility in water is not well defined (Milians, D430751, 06/23/2016). It is not expected to volatilize significantly due to the compound's low vapor pressure of 9.8×10^{-25} torr (25°C). It is considered to be moderately to hardly mobile and to preferentially sorb to soils with minimal expected transport in the dissolved phase in runoff or leachate. However, it can be present in erosion runoff.

Oxytetracycline hydrolysis occurs at a half-life of 2.95 days and is susceptible to degradation by aquatic photolysis ($t_{½}$ = 0.04 days). It is non-persistent (Goring scale, 1975) in aerobic soils ($t_{½}$ = 16.8, 15.3, 11.8 and 13.3 days, MRID 49727801). Stability is assumed for aerobic and anaerobic aquatic environments because no data is available.

3.3 Pesticide Use Pattern

Oxytetracycline is a broad-spectrum antibiotic produced from the bacterium *Streptomyces rimosus*. The antibiotic is a human and animal drug that is used primarily to control bacteria, fungi, and mycoplasma-like organisms.

Proposed Uses
The proposed uses of Oxytetracycline Technical (EPA Reg No. 71185-5) and FireLine 17 WP (EPA Reg. No. 80990-1) are to control Huanglongbing (HLB) (citrus greening disease) and/or Citrus Canker on citrus crops. The proposed use pattern for FireLine 17 WP consists of up to three foliar ground applications to citrus with a maximum single application rate of 0.255 lb oxytetracycline/A. Applications are expected to be made *via* aerial and airblast equipment.

The proposed labels require occupational handlers to wear long-sleeved shirts, long pants, chemical-resistant gloves made of any waterproof material, shoes plus socks, and protective eyewear. The proposed labels list a 12-hour restricted entry interval (REI).

Registered Uses
Oxytetracycline is also registered for use on apple, peach, nectarine, and ornamental trees as a foliar spray and a tree/trunk injection. Maximum single application rates for foliar sprays range from 0.275 lb oxytetracycline HCl/A to 0.903 lb oxytetracycline HCl (0.255 lb oxytetracycline/A to 0.833 lb oxytetracycline/A). Application rates for tree injections range from 0.014 lb ai/tree to 0.0008 lb ai/tree. Applications are expected to be made *via* tree injection, airblast, and handheld equipment.

PPE includes long-sleeved shirts, long pants, shoes plus socks, protective eyewear, chemical resistant gloves, and a dust/mist filtering respirator (Mine Safety and Health Administration (MSHA)/ National Institute for Occupational Safety and Health (NOISH) approval number prefix TC-21C) or a NIOSH approved respirator with any N, R, P or HE filter. The registered labels list a 12-hour REI.

Table 3.3 provides a summary of the proposed and registered uses of oxytetracycline.

Table 3.3. Summary of Directions for Proposed and Registered Uses of Oxytetracycline[+].

Use Site	Application Equipment	Formulation / Product [EPA Reg. No.] / Percent AI	Maximum Proposed/Registered Application Rate	PHI (days)	Use Directions and Limitations
Proposed Uses of Oxytetracycline					
Citrus	Aerial and airblast	FireLine™ 17 WP (80990-1) 18.3% Oxytetracycline HCl (equivalent to 17% Oxytetracycline)	0.275 lb Oxytetracycline HCl/A (equivalent to 0.255 lb Oxytetracycline/A)	40	Allow minimum of 21 days between applications. Do not use product through irrigation system. Not used for medical or veterinary purposes.
Registered Uses of Oxytetracycline					
Apples, Pears, Peaches, and Nectarines	Aerial and airblast	Willowood Oxytet 17 WP (87290-25) Fireline 17 WP (80990-1) 18.3% Oxytetracycline HCl (equivalent to 17% Oxytetracycline)	0.275 lb Oxytetracycline HCl/A (equivalent to 0.255 lb Oxytetracycline/A)	40	Allow minimum of 21 days between applications. Do not use product through irrigation system. Not used for medical or veterinary purposes.
Apples, Pears, Peaches, and Nectarines	Aerial, airblast, and chemigation	Mycoshield® (55146-97) 17.7% Calcium Oxytetracycline (equivalent to 17% Oxytetracycline)	0.275 lb Oxytetracycline Calcium/A (equivalent to 0.255 lb Oxytetracycline/A)	8	Allow minimum of 21 days between applications.
Ornamental Trees	Tree Injection	Mycoject® Ultra (7946-32) Mycoject® Ultra Hp (7946-33) 4.3% Oxytetracycline HCl	6 mL product every 6 inches of trunk circumference 0.0057 lb ai/tree[1] 0.342 lb ai/day[2]	N/A	Pressurize capsule. Drill tree hole. Combine capsule and feeder tube. Place feeder tube in tree. Remove feeder tube. Do not inject trees that are less than 2 inches in diameter. Not to be used on trees that will produce food within the year following treatment.
Ornamental Trees	Tree Injection	Terrier™ Systemic Antibiotic (69117-10) 4.3% Oxytetracycline HCl	1-2 mL product every 4 inches of trunk circumference 0.0028 lb ai/tree[3] 0.114 lb ai/day[4]	N/A	No drill trunk injection. Chemical injected to cambial area. Do not inject trees that are less than 2 inches in diameter. Not to be used on trees that will produce food within the year following treatment. Not used for medical or veterinary purposes.
Ornamental Trees	Tree Injection	Arbor-OTC (74578-7) 39.60% Oxytetracycline HCl (equivalent to	0.3 fl oz (420 g)/ palm tree 0.05 fl oz ai/5 inches of tree treated 0.0073 lb ai/palm tree[5]	3-4	Use with injection devices. Drill tree hole. Use Arborplugs or Stinger. Not used for medical or veterinary purposes. Use on non-crop bearing ornamentals.

Table 3.3. Summary of Directions for Proposed and Registered Uses of Oxytetracycline+.					
Use Site	**Application Equipment**	**Formulation / Product [EPA Reg. No.] / Percent AI**	**Maximum Proposed/Registered Application Rate**	**PHI (days)**	**Use Directions and Limitations**
		36.7% Oxytetracycline)	4.39 lb ai/day[6] (palm trees) 0.014 lb ai/tree[7] 0.878 lb ai/day[8] (all other trees)		
Ornamental Trees	Tree Injection	Bacastat™ Tree Injection (74779-2) 18.3% Oxytetracycline HCl (equivalent to 17% Oxytetracycline)	0.104 fl oz/bag 0.005 lb ai/tree[9] 0.284 lb ai/day[10]	Bacterial Leaf Scorch: 1 per growing season Lethal Palm Yellows: 4	Use with root flare injection devices including microinjection and macrofusion devices. Do not apply through irrigation system. Only use on trees greater than 6 inches in diameter. Use on non-crop bearing ornamentals.
Ornamental Trees	Tree Injection	Bacastat™ 4.3 (74779-16) 4.3% Oxytetracycline HCl (equivalent to 3.94% Oxytetracycline)	60 mL/tree 0.0008 lb ai/tree[11] 0.0464 lb ai/day[12]	4	Not used for medical or veterinary purposes. Do not apply through irrigation system. Use on non-crop bearing ornamentals. Do not inject trees that are less than 2 inches in diameter. Calculate the number of injection sites by dividing the diameter breast height by 2.
Ornamental Trees	Tree Injection	Arbor Biotic™ (88482-1) 39.60% Oxytetracycline HCl (equivalent to 36.7% Oxytetracycline)	258 g/per 30 palm trees 0.006 lb ai/tree[13] 0.361 lb ai/day[14]	3-4	Drill hole in trunk. Insert injection valve. Draw solution into syringe and inject. Use on non-crop bearing ornamentals. Fruits and nuts from treated trees are not for consumption.

\+ Rates for tree injection were calculated into lb ai/tree and lb ai/day assuming a maximum tree circumference size of 60 inches, that one 60-inch tree could contain 10 or 15 injection sites, and that one occupational handler could treat 600 sites per day

1 (6 mL/6 inch)*(60 inch/tree)*(1 gal/3785.41 mL)*[8.34 lb ai/gal (density of water)]*(4.3% ai)

2 (6 mL/6 inch)*(60 inch/10 sites)*(0.033814 fl oz/1 mL)*(1 gal/128 fl oz)*[8.34 lb ai/gal (density of water)]*(4.3% ai)*(600 sites/day)

3 (2 mL/4 in)*(60 in/tree)*(0.033814 fl oz/mL)*(1 gal/128 fl oz)*[8.34 lb ai/gal (density of water)]*(4.3% ai)

4 (2 mL/4 in)*(60 in/15 sites)*(0.033814 fl oz/mL)*(1 gal/128 fl oz)*[8.34 lb ai/gal (density of water)]*(4.3% ai)*(600 sites/day)

5 (420 g/50 trees)*(0.0022 lb/g)*(39.60% ai)

6 (420 g/50 trees)*(0.0022 lb/g)*(1 tree/1 site)*(600 sites/day)*(39.60% ai)

7 (420 g/500 in)*(20 in/tree)*(0.0022 lb/g)*(39.60% ai)

8 (420 g/500 in)*(20 in/tree)*(1 tree/10 sites)*(0.0022 lb/g)*(600 sites/day)*(39.60% ai)

9 (0.104 oz/bag)*(1 bag/1.5 fl oz of H_20)*(1 lb/16 oz)*(18.30% ai)*(0.3 fl oz/1 in)*(20 in/1 tree)

10 (0.104 oz/bag)*(1 bag/1.5 fl oz of H_20)*(1 lb/16 oz)*(18.30% ai)*(0.3 fl oz/1 in)*(20 in/1 tree)*(10 sites/tree)*(600 sites/day)

11 (60 mL/tree)*)*(1 gal/3785.41 mL)*[8.34 lb ai/gal (density of water)]*(4.3% ai)

12 (60 mL/tree)*(1 tree/10 sites)*(600 sites/day)*(0.033814 fl oz/1 mL)*(1 gal/128 fl oz)*[8.34 lb ai/gal (density of water)]*(4.3% ai)

13 (258 g/30 trees)*(0.0022 lb/g)*(39.60% ai)

14 (258 g/30 trees)*(0.0022 lb/g)*(1 tree/1 site)*(600 sites/day)*(39.60% ai)

3.4 Anticipated Exposure Pathways

Humans may be exposed to oxytetracycline in food and drinking water. Oxytetracycline may be applied directly to growing crops and application may result in oxytetracycline reaching surface and ground sources of drinking water. There are no residential uses of oxytetracycline; therefore, residential handler and post-application exposures related to such residential uses are not expected. There are uses that could result in non-occupational spray drift, leading to the potential for post-application dermal and incidental oral exposures. Occupational uses could result in dermal and inhalation occupational handler and post-application exposures. However, dermal exposure was not assessed because of the low dermal absorption that is expected based on the chemical properties of the compound; therefore, a dermal POD was not selected (See Section 4.2.1).

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (https://www.epa.gov/laws-regulations/summary-executive-order-12898-federal-actions-address-environmental-justice). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the National Health and Nutrition Survey/What We Eat in America (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

4.1 Toxicology Studies Available for Analysis

The oxytetracycline toxicity database has been generated since the 1950's, and additional generic testing for toxicity has been waived (Greear, 3/23/1988, TXR# 0007166). The waiver, however, did not specifically exclude new data requirements established after the waiver was recommended. The most recent toxicology data received was the Guideline Series 870.7800 immunotoxicity study.

The existing database includes:

-National Cancer Institute (NCI) Cancer Studies in Rats and Mice (and supporting 90-day range-finding studies)
-National Toxicology Program (NTP) Subchronic Oral Studies in Rats and Mice
-Chronic Oral Studies in Rats and Dogs
-Developmental Toxicity Studies in Rats and Mice
-Mutagenicity/Genetic Toxicity Studies
-Immunotoxicity Study in Rats
-Special Study: Antimicrobial Resistance in Dogs
-Published literature on the effects of tetracyclines on membranous bone growth and dentin apposition in young/infant rhesus monkeys[1]

HED has concluded that additional toxicity data are not required at this time because the available laboratory animal toxicity data, in conjunction with the conclusions that can be drawn from the decades of use of oxytetracycline as a human antibiotic drug without significant incidents, is sufficient to assess the safety of oxytetracycline; therefore, additional toxicity data have been waived by the agency.

4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

A Guideline Series 870.7485 general metabolism and pharmacokinetics study for oxytetracycline is not available. However, studies in the literature provide insight into the absorption, distribution, metabolism, and elimination of oxytetracycline. Most of the tetracyclines are incompletely absorbed from the gastrointestinal tract. For tetracyclines (oxytetracycline, demeclocycline and tetracycline), 60-80% of an oral dose is absorbed when the stomach is empty (The Pharmacological basis of Therapeutics, 9th Edition, 1996, p. 1126). After oral administration, serum concentrations rise slowly, with absorption occurring in the stomach, duodenum and small intestines. Tetracycline and oxytetracycline C_{max} varies with oral dose concentrations, but has been shown to be 2 mg/L and 3-5 mg/L for 250 mg and 500 mg doses, respectively, with a t_{max} of 2-4 hours. Insoluble complexes are formed with calcium, magnesium, iron and aluminum; protein, fat and carbohydrates reduce the absorption of tetracyclines. The variation of the above factors, along with poor quality tissue distribution data, make it difficult to make firm conclusions on tissue distribution properties (Agwuh and MacGowan, 2006). However, accumulation has been seen in the reticuloendothelial cells of the liver, spleen and bone marrow, and in bone, dentine, and the enamel of unerupted teeth. In 1990, the Joint Expert Committee on Food Additives (JECFA) of the Food and Agriculture Organization/World Health Organization (FAO/WHO) produced a monograph on tetracycline used as a drug in food animals that described the state of understanding of oxytetracycline metabolism in livestock.[2] This report provides additional information to support the conclusion that the residue of concern in livestock and poultry is parent oxytetracycline only and showcases that oxytetracycline is not highly metabolized. Tetracyclines are primarily excreted through the kidney, but are also concentrated in the liver, excreted by the bile, into the intestine, and are

[1] Yen P.K.J and Shaw J.H. Effects of Tetracyclines on Membranous Bone Growth and Dentin Apposition in Young Rhesus Monkeys. Journal of Dental Research. July-August 1974. 53(4): 897-906.
[2] Residues of Some Veterinary Drugs in Animals and Food, FAO Food and Nutrition paper 41/3 1991 ISBN 92-5-103061-8, pp. 97-117.

partially reabsorbed *via* enterohepatic recirculation (The Pharmacological basis of Therapeutics, 9th Edition, 1996, p. 1126). Urinary elimination is 30% for tetracycline while fecal elimination is 20-60% for tetracycline and 50% for oxytetracycline. Half-lives vary with the concentration of oral dose, however, at 250 mg the $t_{1/2}$ for tetracycline and oxytetracycline is 6-11 hours and 9.2 hours, respectively. This supports a plateau-shaped progression with a slow rise and drop (Agwuh and MacGowan, 2006).

4.2.1 Dermal Absorption

There is no Guideline Series 870.7600 dermal absorption study available. The dermal absorption study for oxytetracycline is not critical for risk assessment because of the low dermal absorption that is expected based on the chemical properties of the compound. Oxytetracycline has a high molecular weight (496.47), will ionize at neutral pH and has an octanol-water partition coefficient of -0.90. In addition, several acute dermal studies have been submitted and reviewed for formulation products containing oxytetracycline hydrochloride. The highest percentage of active ingredient in the acute studies that were reviewed was 48.35; it was determined to be a Category III for acute dermal toxicity. The chemical properties of oxytetracycline, along with acute dermal data available for formulation products, indicate that there is limited potential for dermal absorption.

4.3 Toxicological Effects

The tetracyclines are antibiotics that inhibit protein synthesis. Inhibition occurs when oxytetracycline binds to 30S ribosomes, preventing aminoacyl tRNA from reading the mRNA ribosomal complex and thus preventing polypeptide elongation. Bacteria import tetracyclines through the inner cytoplasmic membrane of the cell, while mammalian cells have shown poor accumulation of the antibiotic (Franklin, 1966). This results in sensitivity differences at the ribosomal level between bacteria and mammals.

In the animal toxicity database established for the use of oxytetracycline as a pesticide, fatty metamorphosis of the liver is seen in the rat chronic toxicity/carcinogenicity study. Decreases in body weight are seen in the mouse 90-day oral subchronic study and the mouse carcinogenicity study. In the rat oral subchronic study and the mouse prenatal development study, no adverse effects are seen at doses that exceed the limit dose. The Guideline Series 870.7800 rat immunotoxicity study demonstrated immunosuppression at doses lower than those for systemic toxicity. Systemic effects were not observed up to the HDT (479 mg/kg/day), while immunotoxicity effects were seen at 479 mg/kg/day. The immunotoxicity NOAEL is therefore 93 mg/kg/day.

The maternal effects in the rat prenatal development study included an increased incidence of respiratory signs (wheezing and dyspnea), rough hair coat, increased mortality (6%), and a decrease in the percentage of treated dams found pregnant at sacrifice (23% vs. 32% in the controls). Developmental effects included decreased fetal body weight (12%). In all of the above studies, adverse effects were seen at levels that exceed the limit dose. Oxytetracycline is known to inhibit bone growth in developing tissue. When oxytetracycline was administered

orally, as a single dose, to two female infant rhesus monkeys, zygomatic arch bone (lateral surface of temporal bone) growth was inhibited for ~12.5 days with no recovery observed by 21 days. Effects on bone growth are consistent with oxytetracycline's ability to chelate calcium, and so are not unexpected.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)

The toxicity database for oxytetracycline is considered complete. The exposure database is complete, and exposure estimates are likely to overestimate actual exposures from dietary (food and drinking water) sources. Within the toxicity database, the mouse prenatal development study did not identify adverse effects up to the HDT, 2100 mg/kg/day. In addition, the effects seen in the rat prenatal development study occurred at levels above the limit dose. Maternal effects included an increased incidence of respiratory signs (wheezing and dyspnea), rough hair coat, increased mortality (6%), and a decrease in the percentage of treated dams found pregnant at sacrifice (23% vs. 32% in the controls). Developmental effects included decreased fetal body weight (12%). The chronic dietary point of departure (POD) is established on the no adverse effects in the chronic rat (NOAELs = 50 mg/kg/day and 150 mg/kg/day) and dog (NOAEL = 250 mg/kg/day) studies and on levels that exceed the limit dose in the rat chronic toxicity/carcinogenicity study.

Oxytetracycline is known to inhibit bone growth in developing tissue. In a published literature study, two infant rhesus monkeys were given six weekly injections of lead acetate at 3 mg/kg/bw as an intravital stain. With the third dose of lead acetate, one oral dose of 80 mg/kg/bw oxytetracycline was administered. Animals were sacrificed and small segments on bone containing coronal, sagittal, lambdoidal, and zygomaticotemporal sutures were removed in addition to several types of teeth. By measuring the insoluble black lead sulfide at calcification sites, created by saturating the tissue with hydrogen sulfide, it was possible to determine if bone and/or tooth growth was inhibited. Oral administration of oxytetracycline inhibited zygomatic arch bone (lateral surface of temporal bone) growth for ~12.5 days with recovery incomplete by 21 days. Bone developmental effects were also observed after administration of chlortetracycline and demethylchlortetracycline in adult rhesus monkeys highlighting the consistency of tetracycline treatment across this class of chemicals. Dentinogenisis was not affected after administration of any of the tested tetracyclines. Given the bone delay observed in infant monkeys, HED concludes that there remains uncertainty regarding potential sensitivity to infants, children, and pregnant women, which requires that the 10X FQPA SF be retained to assure adequate protection for these populations.

HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (https://www.epa.gov/children/epas-policy-evaluating-risk-children).

4.4.1 Completeness of the Toxicology Database

The existing database, together with the literature on oxytetracycline, are considered adequate for characterizing toxicity and quantification of risk from the proposed and existing uses of oxytetracycline.

4.4.2 Evidence of Neurotoxicity

There are no indications of neurotoxicity in the limited animal studies and it does not appear as an off-target effect in human clinical applications.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

Although the guideline toxicity studies did not suggest an increased lifestage sensitivity/susceptibility (effects above the limit dose or no effects at the highest doses tested), data from the literature suggests that developing infants and children may be more susceptible to oxytetracycline side-effects than adults. As noted in Section 4.4, oxytetracycline inhibited bone growth in infant rhesus monkeys; therefore, the 10X FQPA SF is being retained to protect sensitive population groups.

In the previous human health risk assessments supporting the DRA for oxytetracycline, EPA cited to a study showing that premature infants exposed to oxytetracycline experience delays in bone growth in order to support the retention of a 10X safety factor. This resulted in a chronic Population Adjusted Dose (cPAD) of 0.1 mg/kg/day. EPA concluded that the study is not needed in order for EPA to conduct its risk assessment for this pesticide product. More specifically, EPA scientists identified a study in infant monkeys showing that adverse effects occurred at a lower dose than EPA identified previously (80 mg/kg/day vs 100 mg/kg/day) (Yen P.K.J and Shaw J.H. Effects of Tetracyclines on Membranous Bone Growth and Dentin Apposition in Young Rhesus Monkeys. Journal of Dental Research. July-August 1974. 53(4): 897-906). EPA is relying on the results of that study, along with oxytetracycline's known ability to chelate calcium, to retain the 10X FQPA safety factor. This results in EPA's establishment of a more protective cPAD for dietary risk assessment.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties with regard to the exposure database. The dietary assessment overestimates actual exposures to oxytetracycline as it incorporated tolerance-level residues, default processing factors (PFs), assumed that 100% of the proposed and existing crops are treated with oxytetracycline, and included high-end ground and surface drinking water modeling estimates. All of the exposure and risk estimates are based on assumptions that are likely to overestimate exposures that are actually received.

4.5 Toxicity Endpoint and Point of Departure Selections

4.5.1 Dose-Response Assessment

A detailed description of the toxicity studies used for selecting toxicity endpoints and points of departure for various exposure scenarios is presented in Appendix A.

An acute endpoint was not selected for the general population including females age 13-49 as no adverse effects attributed to a single exposure were identified. The results observed in the monkey study with oxytetracycline are not considered an adverse acute effect. The delayed bone growth occurs as a result of chelation of calcium, the mineral needed for bone growth. When the monkeys are treated with a very high dose of oxytetracycline (80 mg/kg), the calcium can be bound up for several days, leading to a delay in bone growth during that short time frame. However, once the oxytetracycline levels diminish, bone growth continues resulting in normal bones at maturity.

Previously, the endpoint for chronic dietary exposure was established on alterations in intestinal flora based on a special dog study that demonstrated a NOAEL of 0.05 mg/kg/day. However, the Toxicology Science Advisory Committee (ToxSac) meeting on September 1, 2011 concluded the following: "In keeping with the National Academy of Science (NAS)[3] report, the Agency has based its endpoint selection on biologic perturbations of toxicity pathways that can lead to adverse health outcomes under conditions of human exposure." In the absence of a demonstrable adverse health outcome, the Agency did not consider the changes in intestinal flora to be appropriate for conducting a quantitative risk assessment.

The Registration Standard (Greear, 3/23/1988, TXR# 0007166) determined that the Provisional acceptable daily intake (ADI) [3] (PADI) was based on the results of four chronic studies (MRIDs: 00132394 and 00132395). HED determined that the NOAEL for the chronic dietary endpoint should be 100 mg/kg/day, consistent with the recommendation made in the Registration Standard based on the chronic toxicity studies in the rat and dog as noted above, plus the NCI rat chronic toxicity/carcinogenicity study (MRID 00159856).

A chronic dietary endpoint was selected using a WOE approach with a NOAEL of 100 mg/kg/day based on no adverse effects (See Section A.3) in the rat (NOAELs = 50 and 150 mg/kg/day) and dog (NOAEL = 250 mg/kg/day) chronic feeding studies; the highest dose tested in all studies. In the NCI rat chronic carcinogenicity study, the LOAEL was 1250 mg/kg/day (LDT) based on fatty metamorphosis and increases in accessory structures of the liver. HED recommended the inclusion of the customary 100X UF for both interspecies and intraspecies variability resulting in a chronic reference dose (cRfD) of 1.0 mg/kg/day. The FQPA SF of 10X has been retained resulting in a cPAD of 0.1 mg/kg/day.

The short-term incidental oral and inhalation endpoints for risk assessment were selected from the same chronic toxicity studies in the rat and dog as described above, using the same NOAEL as used for chronic dietary assessment (100 mg/kg/day).

Appendix A.3 includes summaries of the studies used for endpoint selection. The four studies that were conducted circa 1959-1962 in rats and dogs would not meet current criteria for guideline acceptability because: 1) of the absence of individual animal data, 2) the strain of dog tested was not consistent between studies, 3) different formulations of oxytetracycline or tetracycline were tested, and 4) only males were included in certain studies. Therefore, these

[3] Toxicity testing in the 21st century: A vision and a strategy. National Academy of Sciences Press (2007), page 46.

[3] The acceptable daily intake (ADI) is defined as the daily intake of oxytetracycline, during the entire lifetime, which appears to be without appreciable risk.

studies were classified as supplementary (Greear, 3/23/1988, TXR# 0007166). The NCI rat carcinogenicity study was classified as minimum (Greear, 3/23/1988, TXR# 0007166). The need for additional testing to verify any of the apparent treatment related alterations was waived in the Registration Standard (Greear, 3/23/1988, TXR# 0007166), sustained in the Tolerance Reassessment Progress and Risk Management Decision (TRED; Donovan, 2/6/2006, D315686), the most recent Human Health Risk Assessment (Negrón-Encarnación, 2/16/2012, D381394), and the current assessment.

A decrease in body weight was seen in several studies within the database, in addition to the maternal effects in the prenatal development study in the rat, but occurred at doses that are approximately 12X-750X higher than the POD used in endpoint selection. Therefore, the endpoint selected for risk assessment is protective of the body weight, maternal and liver effects seen within the database. The rat immunotoxicity study did not detect systemic effects up to the HDT, but immune system changes were observed at 429 mg/kg/day (mild to moderate decreases in mean absolute splenocyte viability, specific activity and total activity; suppression of anti-SRBC antibody response). The selected chronic dietary POD is protective of the immune effects; the NOAEL at 93 mg/kg/day is a reflection of the dose-spacing of the study (LOAEL 429 mg/kg/day).

A dermal endpoint has not been selected for the current assessment due to the low dermal absorption that is expected based on the chemical properties of oxytetracycline (See Section 4.2.1). In addition, no endpoint attributable to a single exposure was identified for females age 13-49 or for the general population from the available oral toxicity database. Therefore, an acute endpoint was not selected for the current risk assessment.

4.5.2 Recommendation for Combining Routes of Exposures for Risk Assessment

If the toxicity endpoints and PODs for dermal, oral, and inhalation routes of exposure are similar the exposure or risk estimates from these exposure routes need to be combined. In the case of oxytetracycline, dietary and incidental oral routes of exposure can be combined for non-occupational exposure.

4.5.3 Cancer Classification and Risk Assessment Recommendation

The RfD/Peer Review Committee (Ghali, 12/4/1992, TXR# 0051521) concluded that the doses tested in the rat and mice are adequate for carcinogenicity testing (2500 mg/kg/day in rats; 1875 mg/kg/day in mice), and the data evaluation records for these two studies are adequate. Oxytetracycline was classified as a "Group D: Not Classifiable as to Human Carcinogenicity".

This classification is in agreement with the conclusion made by the NTP Peer Review Committee. NTP concluded there was equivocal evidence of carcinogenicity for male F344/N rats in the high dose group, as indicated by increased incidences of pheochromocytomas of the adrenal gland (with a statistically significant positive trend, not significant in pairwise comparison with concurrent controls, and was outside the historical control range). There was equivocal evidence of carcinogenicity for female F344/N rats as indicated by increased incidences of adenomas of the pituitary gland in the high dose group, based on a high

background rate. NTP concluded that there was no evidence of carcinogenicity for male or female B6C3F1 mice fed oxytetracycline hydrochloride for two years.

Given the equivocal nature of the carcinogenic response in the rat study at an extremely high dose level, particularly when the actual dietary exposure to humans is taken into consideration, and the fact that mutagenicity data were inconclusive, the RED cRfD/Peer Review Committee felt that the "D Group" classification was appropriate. This classification is based on adequate studies in two animal species and new carcinogenicity studies are not needed at this time; however, this topic may be revisited if the use pattern changes.

4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.4.1 Summary of Toxicological Doses and Endpoints for Oxytetracycline for Use in Dietary and Non-Occupational Human Risk Assessments

Exposure Scenario	Point of Departure	UF/FQPA SF	RfD, PAD, LOC for Risk Assessment	Study and Toxicological Effects
Acute Dietary (all populations)	None selected	NA	NA	No appropriate endpoint for females age 13-49 or for the general population attributable to a single exposure.
Chronic Dietary (all populations)	NOAEL = 100	FQPA SF = 10X UF_H = 10 UF_A = 10	cRfD = 1 mg/kg/day cPAD = 0.10 mg/kg/day	WOE from 3 rat and 2 dog chronic studies. The NOAEL of 100 mg/kg/day was derived from these studies and no specific LOAEL was established.
Incidental Oral (Short-term)	NOAEL = 100	FQPA SF = 10X UF_H = 10 UF_A = 10	cRfD = 1 mg/kg/day cPAD = 0.10 mg/kg/day	WOE from 3 rat and 2 dog chronic studies. The NOAEL of 100 mg/kg/day was derived from these studies and no specific LOAEL was established.
Dermal	None selected	N/A	N/A	Dermal endpoint was not selected based on the chemical properties of oxytetracycline (See Section 4.2.1).
Cancer Classification (oral, dermal, inhalation): The Agency's Peer Review Committee has classified oxytetracycline as a "Group D carcinogen: Not Classifiable as to Human Carcinogenicity".				

Table 4.5.4.2. Summary of Toxicological Doses and Endpoints for Oxytetracycline for Use in Occupational Human Risk Assessments				
Exposure Scenario	**Point of Departure**	**UF/FQPA SF**	**RfD, PAD, LOC for Risk Assessment**	**Study and Toxicological Effects**
Inhalation (Short and Intermediate-term)	NOAEL = 100	Database UF = 10X UF_H = 10 UF_A = 10	Occupational LOC for MOE < 1000	WOE from 3 rat and 2 dog chronic studies. The NOAEL of 100 mg/kg/day was derived from these studies and no specific LOAEL was established.
Dermal	None selected	N/A	N/A	Dermal endpoint was not selected based on the chemical properties of oxytetracycline (See Section 4.2.1).
Cancer Classification (oral, dermal, inhalation): The Agency's Peer Review Committee has classified oxytetracycline as a "Group D carcinogen: Not Classifiable as to Human Carcinogenicity".				

UF = uncertainty factor, UF_A = extrapolation from animal to human (interspecies), UF_H = potential variation in sensitivity among members of the human population (intraspecies), FQPA SF = FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic), RfD = reference dose (a = acute, c = chronic), MOE = margin of exposure, LOC = level of concern, WOE= weight of evidence, NA = Not Applicable, HDT = highest dose tested.

4.6 Endocrine Disruption

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of the most recent registration decision for oxytetracycline, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), oxytetracycline is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect

produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[1] and includes some pesticides scheduled for registration review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[2]

[1] See https://www.epa.gov/endocrine-disruption/overview-second-list-chemicals-tier-1-screening-under-endocrine-disruptor for the final second list of chemicals.
[2] http://www.epa.gov/endo/

5.0 Dietary Exposure and Risk Assessment

5.1 Metabolite/Degradate Residue Profile

The 1988 Registration Standard determined that while the use of oxytetracycline is very limited on crops, metabolism data are not required because it is a widely used human and animal drug. HED therefore concluded that the residue of concern for plants and livestock is parent oxytetracycline only (Table 5.1). In 1990, the Joint Expert Committee on Food Additives (JECFA) of the Food and Agriculture Organization/World Health Organization (FAO/WHO) produced a monograph on tetracycline used as a drug in food animals that described the state of understanding of oxytetracycline metabolism in livestock.[4] This report provides additional information to support the 1988 Registration Standard conclusion that the residue of concern in livestock and poultry is parent oxytetracycline only.

Table 5.1. Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression.

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Oxytetracycline	Oxytetracycline
	Rotational Crop	Not Applicable	Not Applicable
Livestock	Ruminant	Oxytetracycline[1]	Not Applicable[1]
	Poultry		
Drinking Water		Oxytetracycline	Not Applicable

[1] The tolerances in livestock are set by FDA for animal drug uses. The term "tetracyclines" is used because FDA has set one tolerance to cover three tetracyclines (chlortetracycline, oxytetracycline, and tetracycline). These tolerances are established in the 21 CFR §556.500 for the uncooked edible tissues of beef cattle, dairy cattle, calves, swine, sheep, chicken, turkey, finfish, and lobster.

5.2 Food Residue Profile

Adequate residue chemistry data have been provided for oxytetracycline. Field trials for oxytetracycline are of an adequate number and geographic representation. Data analyses for oxytetracycline are all performed with validated analytical methods and are supported by adequate storage stability data. Residues are generally low in raw agricultural commodities (RACs) treated with oxytetracycline and they have not been found to concentrate in processed commodities. The LOQ for all citrus commodities proposed in the current action is 0.01 ppm. The magnitude of the residue data provided to support the current petition indicate that when following the proposed use pattern, detectable residues of oxytetracycline are not expected in citrus RACs. Empirical processing data indicate that no residues of oxytetracycline were found in citrus RACs or its processed commodities, following treatment at an exaggerated rate of 3X. Thus, no separate tolerances are needed for processed commodities from citrus. Because there is

[4] Residues of Some Veterinary Drugs in Animals and Food, FAO Food and Nutrition paper 41/3 1991 ISBN 92-5-103061-8, pp. 97-117.

no reasonable expectation of finite residues in livestock, oxytetracycline remains under category 3 of 40 CFR 180.6(a). Rotational crop data are not required for oxytetracycline because it is not used on crops that are grown in rotation. Recommended tolerances are based on the method LOQ for the analyzed citrus matrices. No additional residue chemistry data are required.

5.3 Water Residue Profile

Residues of oxytetracycline are concluded to be stable in aquatic environments and can reach drinking water supplies for human consumption through applications made as a pesticide to crops. As a result, the Environmental Fate and Effects Division (EFED) provided drinking water exposure estimates for risk assessment The drinking water residues used for dietary risk assessment are summarized in the EFED memorandum, "Drinking Water Assessment for the Registration Review and New Use of Oxytetracycline on Florida Citrus" (Milians, 06/23/2016, D430751). Water residues were incorporated in the Dietary Exposure Evaluation Model-Food Commodity Intake Database (DEEM-FCID) into the food categories "water, direct, all sources" and "water, indirect, all sources."

The estimated drinking water concentration (EDWC) for the chronic assessment was estimated using the Pesticide in Water Calculator (PWC v.1.52). PWC uses the Pesticide Root Zone Model (PRZM) version 5.02 and the Variable Volume Water Body Model (VVWM V1.02) to estimate concentrations in surface water. The ground water EDWCs were assessed using PRZM-Ground Water (PRZM-GW). The models used to derive the EDWCs are listed in Table 5.3. The models and their descriptions are available at the EPA internet site: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/about-water-exposure-models-used-pesticide.

Table 5.3. Tier II EDWCs for resulting from applications of oxytetracycline for surface water and groundwater.*

Model	Use (modeled rate)	1-in-10 year acute (µg/L)	1-in-10 year chronic (µg/L)	30- year average (µg/L)
Pesticide in water calculator	citrus (ground, 0.270 lb a.i./A x 3 application; total of 2.04 lb/A/yr.)	11.0	0.446	0.322
	peaches and nectarines (ground, 0.638 lb a.i./A x 9 application; total of 5.74 lbs/A/yr.)	117	**2.85 (0.00285 ppm)**	2.02
Ground Water numbers	peaches and nectarines (ground, 0.638 lb a.i./A x 9 application; total of 5.74 lbs/A/yr.)	0.323	0.323	0.323

* Bolded values represent the recommended EDWCs for HED

5.4 Dietary Risk Assessment

5.4.1 Description of Residue Data Used in Dietary Assessment

Established and proposed tolerance-level residues were used in the chronic dietary exposure assessment. In conjunction with the FDA-approved animal drug uses, food-additive tolerances are established for residues of tetracyclines in commodities of beef cattle, dairy cattle, calves,

swine, sheep, chickens, turkeys, finfish, and lobster up to 12 ppm (21 CFR §556.500) and were included in the dietary exposure assessment. The chronic dietary exposure assessment assumed that 100% of the proposed and registered crops were treated with oxytetracycline. Default processing factors (PFs) were used for all processed commodities, except citrus juice, oil, and peel since concentration is not expected (i.e. empirical PFs <1X). The default PFs included in the dietary exposure assessment are as follows: 8.0X (apple, dried; apple, dried, baby food); 6.25X (pear, dried); 7.0X (peach, dried; peach, dried baby food); and 1.92X (beef, meat, dried). Tolerances for livestock and fish commodities resulting from the use of oxytetracycline as an animal drug were also included in the dietary exposure assessment.

5.4.2 Acute Dietary Risk Assessment

An acute dietary assessment was not conducted since an acute endpoint is not considered appropriate. No appropriate endpoint attributable to a single exposure was identified in the toxicity database.

5.4.3 Chronic Dietary Risk Assessment

Unrefined chronic dietary assessments were conducted using tolerance-level residues, 100% CT assumptions, default PFs, and screening-level EDWCs. The estimated risk is 11% of the cPAD for the general U.S. population. The subpopulation with the highest risk estimates are children 1-2 years old (33% of the cPAD). The results for all standard population subgroups are summarized in Table 5.4.5

5.4.4 Cancer Dietary Risk Assessment

Oxytetracycline was classified as "Not Classifiable as to Human Carcinogenicity"; therefore, a cancer dietary assessment has not been completed.

5.4.5 Summary Table

Table 5.4.5. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Oxytetracycline.

Population Subgroup	Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% cPAD*
General U.S. Population	0.010648	11
All Infants (<1 year old)	0.011089	11
Children 1-2 years old*	**0.033445**	**33**
Children 3-5 years old	0.025678	26
Children 6-12 years old	0.016392	16
Youth 13-19 years old	0.010010	10
Adults 20-49 years old	0.008851	8.9
Adults 50-99 years old	0.007371	7.4
Females 13-49 years old	0.007785	7.8

*The subpopulation with the highest risk estimates.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

There are no proposed or registered residential uses of oxytetracycline; therefore, a residential assessment has not been performed. A turf transferrable residue (TTR) study is not required for oxytetracycline at this time because there are no proposed or registered uses on turf.

7.0 Non-Occupational Spray Drift Exposure and Risk Estimates

Spray drift is a potential source of exposure to those nearby pesticide applications. This is particularly the case with aerial application, but, to a lesser extent, spray drift can also be a potential source of exposure from the ground application methods (e.g., groundboom and airblast) employed for oxytetracycline. The Agency has been working with the Spray Drift Task Force (a task force composed of various registrants which was developed as a result of a Data Call-In issued by EPA), EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices (see the Agency's Spray Drift website for more information). [5] The Agency has also developed a policy on how to appropriately consider spray drift as a potential source of exposure in risk assessments for pesticides. The potential for spray drift will be quantitatively evaluated for each pesticide during the *Registration Review* process which ensures that all uses for that pesticide will be considered concurrently. The approach is outlined in the revised (2012) *Standard Operating Procedures for Residential Risk Assessment (SOPs) - Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift.* This document outlines the quantification of indirect non-occupational exposure to drift.

Off-target movement of pesticides can occur *via* many types of pathways and it is governed by a variety of factors. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those it may directly contact. They can also deposit on surfaces where contact with residues can eventually lead to indirect exposures (*e.g.*, children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling onto 50 feet wide lawns coupled with methods employed for residential risk assessments for turf products. The approach to be used for quantitatively incorporating spray drift into risk assessment is based on a premise of compliant applications which, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to prevent them.[6] Direct exposures would include inhalation of the spray plume or being sprayed directly. Rather, the exposures addressed here are thought to occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted. Given this premise, exposures for children (1 to 2 years old) and adults who have contact with turf where residues are assumed to have deposited *via* spray drift thus resulting in an indirect exposure are the focus of this analysis analogous to how exposures to turf products are considered in risk assessment.

In order to evaluate the drift potential and associated risks, an approach based on drift modeling coupled with techniques used to evaluate residential uses of pesticides was utilized. Essentially, a

[5] Available: http://www2.epa.gov/reducing-pesticide-drift

[6] This approach is consistent with the requirements of the EPA's Worker Protection Standard.

residential turf assessment based on exposure to deposited residues has been completed to address drift from the agricultural applications of oxytetracycline. In the spray drift scenario, the deposited residue value was determined based on the amount of spray drift that may occur at varying distances from the edge of the treated field using the AgDrift (v2.1.1) model and the *Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift Policy*. Once the deposited residue values were determined, the remainder of the spray drift assessment was based on the algorithms and input values specified in the recently revised (2012) *Standard Operating Procedures for Residential Risk Assessment (SOPs)*.
A screening approach was developed based on the use of the AgDrift model in situations where specific label guidance that defines application parameters is not available.[7,8] AgDrift is appropriate for use only when applications are made by aircraft, airblast orchard sprayers, and groundboom sprayers. When AgDrift was developed, a series of screening values (i.e., the Tier 1 option) were incorporated into the model and represent each equipment type and use under varied conditions. The screening options specifically recommended in this methodology were selected because they are plausible and represent a reasonable upper bound level of drift for common application methods in agriculture. These screening options are consistent with how spray drift is considered in a number of ecological risk assessments and in the process used to develop drinking water concentrations used for risk assessment. In all cases, each scenario is to be evaluated unless it is not plausible based on the anticipated use pattern (e.g., herbicides are not typically applied to tree canopies) or specific label prohibitions (e.g., aerial applications are not allowed). Section 6.1 provides the screening level drift related risk estimates. In many cases, risks are of concern when the screening level estimates for spray drift are used as the basis for the analysis. In order to account for this issue and to provide additional risk management options additional spray drift deposition fractions were also considered. These drift estimates represent plausible options for pesticide labels

The spray drift risk estimates are based on an estimated deposited residue concentration as a result of the screening level agricultural application scenarios. Oxytetracycline is used on apples, pears, peaches, nectarines, and citrus and can be applied *via* airblast and aerial equipment. The recommended drift scenario screening level options are listed below:

- **Orchard airblast applications** are based on the AgDrift option for Sparse (Young/Dormant) tree canopies.

- **Aerial applications** are based on the use of AgDrift Tier 1 aerial option for a fine to medium spray type and a series of other parameters which will be described in more detail below (e.g., wind vector assumed to be 10 mph in a downwind direction for entire application/drift event).[9]

[7]http://www.agdrift.com/
[8] Note that for many cases the scenarios outlined in the screening approach represent actual use practice so risk assessors should be aware and characterize these appropriately.
[9] AgDrift allows for consideration of even finer spray patterns characterized as very fine to fine. However, this spray pattern was not selected as the common screening basis since it is used less commonly for most agriculture. If assessors identify this use pattern it should be used as the screening criteria and deposition values associated with it are provided in Table 1 below. Justification for including this spray quality should be included in any assessment based on specific label directions for its use.

Exposures were considered for 50 feet wide lawns where the nearest side of the property was directly adjoining the treated field (at field edge) and at varied distances up to 300 feet downwind of a treated field. Results are presented in Table 7.1 and indicate that hand to mouth risks are not of concern from field edge (MOE >1000) for groundboom, airblast, and aerial applications. Dermal risks were not calculated as a dermal toxicological endpoint was not selected.

Table 7.1. Children (1<2 years old) Risk Estimates (MOEs) Related to Indirect Exposure to Spray Drift for Oxytetracycline for the Incidental Oral Route of Exposure

Crop/Rate Group	Spray Type/ Nozzle Configuration	Appl. Rate (lb ai/A)	TTR (ug/cm2)[1]	Incidental Oral MOE at Field Edge (LOC = 1000)
Aerial	***Fine to Medium***	0.275	0.03056625	93000
Airblast	***Sparse***			170000

1 TTR value calculated based on application rate

8.0 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (https://www.epa.gov/reducing-pesticide-drift/pesticide-volatilization). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (https://www.regulations.gov/document?D=EPA-HQ-OPP-2014-0219-0002). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for oxytetracycline.

9.0 Occupational Exposure/Risk Characterization

9.1 Occupational Handler Exposure/Risk Estimates

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Based on the use profile outlined in section 3.3 above, the quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios:

- Apple, Pears, Peaches, Nectarines, and Citrus
  - Mixing/loading liquids for aerial application
  - Mixing/loading liquids for airblast application
  - Mixing/loading liquids for chemigation

  - Applying liquids for aerial application
  - Applying liquids for airblast application
  - Flagger scenario for aerial application
- Tree Injection
  - Mixing/loading liquids for tree injection

Occupational Handler Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Each assumption and factor is detailed below.

Application Rate: The application rates used in this assessment are shown in Table 3.3.

Unit Exposures: It is the policy of HED to use the best available data to assess handler exposure. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include PHED 1.1, the AHETF database, the Outdoor Residential Exposure Task Force (ORETF) database, or other registrant-submitted occupational exposure studies. Some of these data are proprietary (e.g., AHETF data), and subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures", are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table[10]", which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at the Agency website[11].

Area Treated or Amount Handled: The inputs for area treated or amount of solution or product handled were based on ExpoSAC Policy 9.1

Exposure Duration: HED classifies exposures from 1 to 30 days as short-term and exposures 30 days to six months as intermediate-term. Exposure duration is determined by many things, including the exposed population, the use site, the pest pressure triggering the use of the pesticide, and the cultural practices surrounding that use site.

For oxytetracycline, based on the proposed and registered uses, short- and intermediate-term exposures are expected because for most agricultural uses, it is reasonable to believe that occupational handlers will not apply the same chemical every day for more than a one-month time frame; however, there may be a large agribusiness and/or commercial applicators who may apply a product over a period of weeks (e.g., completing multiple applications for multiple clients within a region). However, the selected inhalation toxicological endpoint is appropriate to evaluate both short- and intermediate-term exposures. No dermal toxicological endpoint was selected.

Mitigation/Personal Protective Equipment: Estimates inhalation exposure were calculated for baseline level of personal protective equipment (PPE). Baseline attire is defined as a single layer

[10] Available: http://www2.epa.gov/sites/production/files/2015-09/documents/handler-exposure-table-2015.pdf
[11] Available: http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

of clothing consisting of a long-sleeved shirt, long pants, shoes plus socks, no protective gloves, and no respirator. The oxytetracycline proposed product labels direct mixers, loaders, applicators and other handlers to wear coveralls over long sleeved shirt and long pants, chemical resistant gloves made of any waterproof material, shoes plus socks, and protective eyewear. The oxytetracycline registered product labels require long-sleeved shirts, long pants, shoes plus socks, protective eyewear, and chemical resistant gloves, and a dust/mist filtering respirator (Mine Safety and Health Administration (MSHA)/ National Institute for Occupational Safety and Health (NOISH) approval number prefix TC-21C) or a NIOSH approved respirator with any N, R, P or HE filter.

Note: Injecting trees is not typically assessed by HED because the Agency has no exposure data for the tree injection application scenario. In this assessment, however, HED did assess exposure from mixing/loading liquids to treat trees with oxytetracycline *via* injection. Use information specific to this chemical was not available for this scenario; therefore, HED used available tree injection assumptions from a previous ORE assessment for dinotefuran (O'Keefe, B., D378123, 2/28/2011) to represent the same scenario. The registered label with the highest application rate (Reg. No. 74758-7) specifies 0.3 fl oz/tree. Based on assumptions of tree size, and number of tree injections an occupational handler could complete per day used in the dinotefuran tree injection assessment, it is assumed that one applicator can make 600 trunk injections per day. This assessment assumes then that the maximum amount of product handled would be 4.39 lb ai/day by one applicator [(420 g/50 trees)*(0.0022 lb/g)*(1 tree/1 site)*(600 sites/day)*(39.60% ai)].

Occupational Handler Non-Cancer Exposure and Risk Estimate Equations

The algorithms used to estimate non-cancer exposure and dose for occupational handlers can be found in Appendix D.

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

Risk estimates for occupational handlers are presented in Table 9.1.1. All handler scenarios resulted in MOEs greater than the LOC (MOEs ≥ 1000), and therefore, these risks are not of concern.

HED has no data to assess exposures to pilots using open cockpits. The only data available are for exposure to pilots in enclosed cockpits. Therefore, risks to pilots are assessed using the engineering control (enclosed cockpits) and baseline attire (long-sleeve shirt, long pants, shoes, and socks); per the Agency's Worker Protection Standard stipulations for engineering controls, pilots are not required to wear protective gloves for the duration of the application. With this level of protection, there are no risk estimates of concern for applicators.

Table 9.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Oxytetracycline							
Exposure Scenario	**Crop or Target**	**Level of Concern**	**Inhalation Unit Exposure (µg/lb ai)[1]**	**Maximum Application Rate[2]**	**Area Treated Daily[3]**	**Inhalation**	
			Baseline			**Dose (mg/kg/day)[4]**	**MOE[5] (LOC = 1000)**
Mixer/Loader							
Aerial	Citrus, Apples, Pears, Peaches, and Nectarines	1000	0.219	0.275 lb ai/acre	350 acres	0.000264	380000
Airblast	Citrus, Apples, Pears, Peaches, and Nectarines	1000	0.219	0.275 lb ai/acre	40 acres	0.0000301	3300000
Chemigation	Apples, Pears, Peaches, and Nectarines	1000	0.219	0.275 lb ai/acre	350 acres	0.000264	380000
Tree Injection	Landscaping, Trees, Nursery (Ornamentals, Trees)	1000	0.219	4.39 lb ai/day	1 day	0.000012	8300000
Applicator							
Aerial	Citrus, Apples, Pears, Peaches, and Nectarines	1000	0.0049	0.275 lb ai/acre	350 acres	0.000472	17000000
Airblast	Citrus, Apples, Pears, Peaches, and Nectarines	1000	4.71	0.275 lb ai/acre	40 acres	0.000748	11000000
Flagger							
Aerial	Citrus, Apples, Pears, Peaches, and Nectarines	1000	0.35	0.275 lb ai/acre	350 acres	0.0337	240000

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (September 2016); Level of mitigation: Baseline
2 Based on registered or proposed label (Reg. No. 80990-1, 87290-25, 55146-97, 74779-2).
3 Exposure Science Advisory Council Policy #9.1.
4 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or lb ai/day) × Area Treated (A or day) ÷ BW (80 kg).
5 Inhalation MOE = Inhalation NOAEL (100 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

9.2 Occupational Post-Application Exposure/Risk Estimates

Occupational post-application dermal exposure was not quantitatively assessed because of the poor dermal absorption expected for oxytetracycline (See Section 4.2.1). Based on the Agency's current practices, a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed for oxytetracycline at this time. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for oxytetracycline. Although a quantitative occupational post-application inhalation exposure assessment was not performed, an occupational inhalation exposure assessment was performed. Handler exposure resulting from the application of pesticides outdoors is likely to result in higher exposure than post-application exposure. Therefore, it is expected that these handler inhalation exposure estimates would be protective of most occupational post-application inhalation exposure scenarios.

10.0 Aggregate Exposure/Risk Characterization

There are no proposed uses which result in residential exposures; therefore, aggregate risk assessments for oxytetracycline consider chronic exposure from food and water only. Since the dietary exposure analysis included both food and drinking water estimates, the exposure and risk estimates presented in Section 5.4.3 represent aggregate chronic exposure and risk. There are no aggregate risks of concern.

Pharmaceutical Aggregate Risk

Section 408 of the FFDCA requires EPA to consider potential sources of exposure to a pesticide and related substances in addition to the dietary sources expected to result from a pesticide use subject to the tolerance. In order to determine whether to maintain a pesticide tolerance, EPA must "determine that there is a reasonable certainty of no harm." Under FFDCA section 505, the Food and Drug Administration reviews human drugs for safety and effectiveness and may approve a drug notwithstanding the possibility that some users may experience adverse side effects. EPA does not believe that, for purposes of the section 408 dietary risk assessment, it is compelled to treat a pharmaceutical user the same as a non-user, or to assume that combined exposures to pesticide and pharmaceutical residues that lead to a physiological effect in the user constitutes "harm" under the meaning of section 408 of the FFDCA. Rather, EPA believes the appropriate way to consider the pharmaceutical use of oxytetracycline in its risk assessment is to examine the impact that the additional non-occupational pesticide exposures would have to a pharmaceutical user exposed to a related (or, in some cases, the same) compound. Where the additional pesticide exposure has no more than a minimal impact on the pharmaceutical user, EPA could make a reasonable certainty of no harm finding for the pesticide tolerances of that compound under section 408 of the FFDCA. If the potential impact on the pharmaceutical user as a result of co-exposure from pesticide use is more than minimal, then EPA would not be able to conclude that dietary residues were safe, and would need to discuss with FDA appropriate measures to reduce exposure from one or both sources.

Tetracycline hydrochloride (97% chemical similarity to oxytetracycline; TOXNET) is approved by the FDA for use as an oral antibiotic to treat certain bacterial and parasitic infections.

Capsules containing the antibiotic are available in 100 mg, 125 mg, 250 mg and 500 mg doses. The average daily dose is 1 g/day - 1.5 g/day and 25 mg/kg/day - 50 mg/kg/day for adults and children above eight years of age, respectively. Typical treatment durations range from 1 week to 1 month and vary depending on the type of infection. Oxytetracycline hydrochloride, in conjugation with polymyxin B sulfate, is also available as a topical ointment at concentrations of 5 mg base/g.

In addition, FDA tolerances up to 12 ppm are established for residues of tetracyclines in commodities of beef cattle, dairy cattle, calves, swine, sheep, chickens, turkeys, finfish, and lobster in tissues; and in milk (21 CFR §556.500).

Table 10.1 provides a comparison of the FDA vs. the EPA approved or proposed tolerances. The exposure to EPA approved oxytetracycline treated agricultural commodities and drinking water containing oxytetracycline, as compared to FDA approved tolerances and therapeutic doses, is low.

Table 10.1: Comparison of FDA vs. EPA Uses of Oxytetracycline

FDA Approved Food-Additive Tolerances (ppm) (21 CFR §556.500)	EPA Approved Tolerances (ppm) (40 CFR §180.337)	EPA Proposed Tolerances (ppm) (40 CFR §180.337)	Highest Drinking Water Exposure for Applications of Oxytetracycline to Citrus (ppm)	Highest Food and Drinking Water Dietary Exposure (ppm)	Recommended Daily FDA Dosage for Children Above 8 years (ppm)	Recommended Daily FDA Dosage for Adults (g)
Cattle, swine, sheep, poultry, finfish, lobster meat: 2.0	Apple: 0.35	Citrus: 0.01	0.00285	Children 1-2 years old: 0.033445	25-50; for a period of 10 days	1 gram; for a period of 1 week- 1 month
Cattle, swine, sheep, poultry, finfish, lobster Liver: 6	Peach: 0.35					
Cattle, swine, sheep, poultry, finfish, lobster Fat/kidney: 12	Pear: 0.35					
Milk: 0.3						

EPA provided its findings with respect to oxytetracycline to FDA in a letter dated February 27, 2018, which is available in the public docket (EPA-HQ-OPP-2015-0820). The pesticidal exposure estimates described in the February 27, 2018 letter reflect the dietary dose from pesticidal uses of oxytetracycline that a user treated with a pharmaceutical oxytetracycline product would receive in a reasonable worst-case scenario. EPA's pesticide exposure assessment has taken into consideration the appropriate population, exposure route, and exposure duration for comparison with exposure to the pharmaceutical use of oxytetracycline. EPA estimates that the pharmaceutical oxytetracycline a user is expected to receive from a typical therapeutic dose (25 mg/kg/day for children) is 750 to 2,800 times greater than the estimated dietary exposure from the pesticidal sources of oxytetracycline (0.0089334 mg/kg/day). FDA responded to EPA in a letter dated April 6, 2018, available the public docket (EPA-HQ-OPP-2015-0820), and

concluded that the pesticide exposures would be negligible when compared to the potential exposure from pharmaceutical use of oxytetracycline, although FDA noted that no oxytetracycline products for systemic use in humans are currently marketed in the United States. Therefore, because the pesticide exposure has no more than a minimal impact on the total dose to a pharmaceutical user, EPA believes that there is a reasonable certainty that the potential dietary pesticide exposure will result in no harm to a user being treated therapeutically with oxytetracycline.

11.0 Cumulative Exposure/Risk Characterization

In 2016, EPA's Office of Pesticide Programs released a guidance document entitled, Pesticide Cumulative Risk Assessment: Framework for Screening Analysis [https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework]. This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs) and conducting cumulative risk assessments (CRA).

The agency has utilized this framework for oxytetracycline and determined that the available toxicological data suggests oxytetracycline does not share a similar toxicological profile with other pesticides. Thus, no further cumulative evaluation is necessary for oxytetracycline.

12.0 Human Incidents Report

Oxytetracycline is being considered under the FQPA-mandated Registration Review program established to review, on a 15-year cycle, pesticides for which a Re-registration Eligibility Decision has been made. One component of the Agency's Registration Review Program is consideration of human incident data. In conjunction with a human health risk assessment based on other data sources, such human incident data can assist the Agency in better defining and characterizing the risk of pesticides/pesticide products.

For this evaluation, both OPP Incident Data System (IDS) and the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH) Sentinel Event Notification System for Occupational Risk-Pesticides (SENSOR) databases were consulted for pesticide incident data on the active ingredient oxytetracycline (PC Codes: 006304, 006308, 006321). The purpose of the database search is to identify potential patterns in the frequency and severity of the health effects attributed to oxytetracycline exposure.
From January 1, 2010 to July 20, 2016, there were no incidents reported for oxytetracycline in either Main or Aggregate IDS.

A query of SENSOR-Pesticides from 1998-2013 identifies a total of three cases involving oxytetracycline. All three cases were occupational cases involving agricultural workers in apple orchards. The three cases involved three separate events in Washington State. All three cases were low in severity. All cases also involved multiple active ingredients. One case involved a farmworker who was thinning apple trees and developed dermal symptoms. This case later

sought medical care and reported skin rash, pain, irritation and edema. Another case is described as follows:

> *The case entered to prune one day after application. The REI of products applied was 12 hours. He entered work at 7:30 AM and by 3:00 PM his hands were itching. The case observed that trees were white in color from the applications. Case's hands and neck started to itch and he sought treatment for dermal irritation and raised rash.*

The final case involved a pesticide handler making an application to an apple orchard using a high pressure ground sprayer. He was wearing safety glasses. He felt the spray hit is face while he was applying. He reported hives on his neck and nasal congestion. However, the registered labels require handlers to wear a dust/mist filtering respirator (Mine Safety and Health Administration (MSHA)/ National Institute for Occupational Safety and Health (NOISH) approval number prefix TC-21C) or a NIOSH approved respirator with any N, R, P or HE filter.

There were no incidents reported to IDS and three low severity cases reported to SENSOR-Pesticides involving oxytetracycline. There does not appear to be a concern at this time. The Agency will continue to monitor the incident data and if a concern is triggered, additional analysis will be conducted.

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Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The requirements (40 CFR §158.340) for food use for oxytetracycline are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table 1: Study Requirements for Food Uses of Oxytetracycline

Study	Technical	
	Required	**Satisfied**
870.1100 Acute Oral Toxicity 870.1200 Acute Dermal Toxicity 870.1300 Acute Inhalation Toxicity 870.2400 Primary Eye Irritation 870.2500 Primary Dermal Irritation 870.2600 Dermal Sensitization	All Studies Waived: • Greear, TXR # 0007166, 3/23/1988 • Donovan, D315686, 2/6/2006 • Soderberg, D353422, 9/12/2008	
870.3100 Oral Subchronic (rat) 870.3150 Oral Subchronic (mouse) 870.3200 21-Day Dermal 870.3250 90-Day Dermal 870.3465 90-Day Inhalation		
870.3700a Developmental Toxicity (rat) 870.3700b Developmental Toxicity (mouse) 870.3800 Reproduction and Fertility Effects (rat)		
870.4100a Chronic Toxicity (rat) 870.4100b Chronic Toxicity (dog) 870.4200a Oncogenicity (rat) 870.4200b Oncogenicity (mouse) 870.4300 Chronic/Oncogenicity (rat)		
870.5100 Mutagenicity—Gene Mutation (bacterial) 870.5195 Mutagenicity—Gene Mutation (mammalian) 870.5375 Mutagenicity—Structural Chromosomal Aberrations 870.5900 Mutagenicity—Sister Chromatid Exchange		
870.6100a Acute Delayed Neurotoxicity (hen) 870.6100b 90-Day Neurotoxicity (hen) 870.6200a Acute Neurotoxicity Screening Battery (rat) 870.6200b 90-Day Neurotoxicity Screening Battery (rat) 870.6300 Develop. Neurotoxicity		
870.7485 General Metabolism 870.7600 Dermal Penetration		
870.7800 Immunotoxicity	Yes	Yes

A.2 Toxicity Profiles

Table A.2.1 Acute Toxicity Profile – Oxytetracycline.				
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.1100	Acute oral [Species: Mouse]	Not known	LD_{50} = 7200 mg/kg	IV
870.1200	Acute dermal	No guideline studies.		
870.1300	Acute inhalation			
870.2400	Acute eye irritation			
870.2500	Acute dermal irritation			
870.2600	Skin sensitization			

Table A.2. Non-Acute Toxicity Profile – Oxytetracycline.		
Study	**MRID No. (year)/ Classification, Doses**	**Results**
870.3150 90-Day Oral Toxicity (mouse)	No MRID NTP study (1986) Supplementary 0, 3100, 6300, 12500, 25000, or 50,000 ppm (0, 465, 945, 1875, 3750, 7500 mg/kg/day; M/F)	NOAEL = 3750 mg/kg/day LOAEL = 7500 mg/kg/day based on decreased body weight
870.3100 90-Day Oral Toxicity (rat)	No MRID NTP study (1986) Supplementary 0, 3100, 6300, 12,500, 25,000 or 50,000 ppm (0, 155, 315, 625, 1250 or 2500 mg/kg/day; M/F)	NOAEL = 2500 mg/kg/day (HDT) LOAEL = Not identified
870.3700a Prenatal Developmental (rat)	00932391 or 00132391 (1983) Oxytetracycline hydrochloride Minimum 0, 1200, 1350, or 1500 mg/kg/day	**Maternal** NOAEL = not identified LOAEL ≤ 1200 mg/kg/day based on increased incidence of respiratory signs and rough hair coat, mortality, and percent of treated dams found pregnant (23% vs 32% in controls) (LDT) **Developmental** NOAEL = not identified LOAEL ≤ 1200 mg/kg/day based on decreased fetal body weights (LDT)
870.3700b Prenatal Developmental (mouse)	00132392 (1982) Oxytetracycline hydrochloride Minimum 0, 1325, 1670, and 2100 mg/kg/day	**Maternal** NOAEL ≥ 2100 mg/kg/day (HDT) LOAEL = not identified. **Developmental** NOAEL ≥ 2100 mg/kg/day (HDT) LOAEL = not identified
870.3800	MRID 00251603 Oxytetracycline hydrochloride	**Parental/Systemic** NOAEL= 18 mg/kg/day (HDT)

Table A.2. Non-Acute Toxicity Profile – Oxytetracycline.		
Study	**MRID No. (year)/ Classification, Doses**	**Results**
Reproduction and Fertility Effects (rat)	**Invalid due to lack of accountability for individual animals and reporting deficiencies** 0 or 360 ppm (0 or 18 mg/kg/day)	LOAEL = not identified **Reproductive** NOAEL and LOAEL > 18 mg/kg/day (HDT) **Offspring** NOAEL = 18 mg/kg/day (HDT) LOAEL = not identified
870.4100a Chronic Toxicity (rat)	MRID 00132394 (1959) and 00132395 (1962) Supplementary **First part:** 0, 1000 or 3000 ppm (0, 5, 50 or 150 mg/kg/day) **Second part:** 0, 100, or 1000 ppm (0, 5, or 50 mg/kg/day)	**First part:** NOAEL = 150 mg/kg/day (HDT) LOAEL = not identified **Second part:** NOAEL = 50 mg/kg/day (HDT) LOAEL = not identified
870.4100 Chronic Toxicity (dog)	MRID 00132394 (1959) and 00132395 (1962) Supplementary **First part:** 0, 100, 3000, or 10000 ppm (0, 2.5, 75, or 250 mg/kg/day) **Second part:** 0, 5000, 10000 ppm (0, 125, or 250 mg/kg/day)	**First part:** NOAEL = 250 mg/kg/day (HDT) LOAEL = not identified **Second part:** NOAEL = 250mg/kg/day (HDT) LOAEL = not identified
870.4200 Carcinogenicity (mouse)	MRID 00159856 (1986) NCI Study Oxytetracycline hydrochloride Minimum 0, 6300, 12500 ppm (0, 945, 1875 mg/kg/day)	NOAEL = 945 mg/kg/day LOAEL = 1875 mg/kg/day based on decreased body weight in male mice **No evidence of carcinogenicity**
870.4300 Combined Chronic Toxicity/ Carcinogenicity (rat)	00159856 (1986) NCI Study Oxytetracycline hydrochloride Minimum 0, 25000, 50000 ppm (0, 1250, or 2500 mg/kg/day)	NOAEL = not identified LOAEL = 1250 mg/kg/day based on fatty metamorphosis of the liver (LDT) **No evidence of carcinogenicity**
870.5100 Bacterial Reverse Mutation Test	No MRID NTP Study Oxytetracycline hydrochloride 0-1µg/ml in DMSO	Negative up to 1µg/plate with or without metabolic activation

Table A.2. Non-Acute Toxicity Profile – Oxytetracycline.		
Study	**MRID No. (year)/ Classification, Doses**	**Results**
870.5195 Mouse Lymphoma Forward Mutation Assay	No MRID NTP Study Oxytetracycline hydrochloride 12.5-800 µg/ml	Concentrations of 100 and 200 µg /ml were mutagenic in L5178Y/TK+/- mouse lymphoma cells, only with metabolic activation
870.5375 Chromosome Aberration Assay (CHO cells)	No MRID NTP Study Oxytetracycline hydrochloride 80-200 µg/ml 700-900 µg/ml	Negative up to 900 µg/ml with or without metabolic activation
870.5900 Sister Chromatid Exchange Assay (CHO cells)	No MRID NTP Study Oxytetracycline hydrochloride 60, 70 and 80 µg/ml 400, 500 and 700 µg/ml	Negative up to 700 µg/ml with or without metabolic activation.
870.7485 Metabolism and Pharmacokinetics (mouse)	Data requirement historically waived. However, a study from open literature is available.	Oral administration of 47.6 mg ^{14}C-labeled hydroxyoxytetracycline monohydrochloride/kg/bw to mice, 72% of the applied dose was found in the large intestine after 2 hours; only 5% was absorbed, of which the major portion (3.6%) was excreted in the urine. In the liver 1.9% and 1.1% of the dose applied was recovered after 1 and 2 hours, respectively.
870.7800 Immunotoxicity (rat)	48759601 (2012) Acceptable/Guideline 0, 133.3, 1333.3, or 6666.7 ppm (0, 9.5, 93, or 479 mg/kg/day)	**Systemic:** NOAEL = 479 mg/kg/day (HDT) LOAEL = NA **Immunotoxicity:** NOAEL = 93 mg/kg/day LOAEL = 479 mg/kg/day
Special study: Antimicrobial Resistance (dog)	40840101 (1975) NTP Study Oxytetracycline 0, 2, or 10 ppm (0, 0.05 or 0.25 mg/kg/day)	NOAEL = 0.05 mg/kg/day LOAEL = 0.25 mg/kg/day based on a shift from a predominantly drug-susceptible population of enteric lactose-fermenting organisms to a multiple antibiotic-resistant population in intestinal flora.
Special Study: Yen P.K.J and Shaw J.H. Effects of Tetracyclines on Membranous Bone Growth and Dentin	Chlortetracycline: 70 mg/kg/bw (oral, IP, IV) Oxytetracycline: 80 mg/kg/bw (oral) Demethylchlortetracycline: 25 mg/kg/bw (oral)	NOAEL/LOAELs not established. Acceptable/non-guideline for qualitative purposes.

Table A.2. Non-Acute Toxicity Profile – Oxytetracycline.		
Study	**MRID No. (year)/ Classification, Doses**	**Results**
Apposition in Young Rhesus Monkeys. Journal of Dental Research. July-August 1974. 53(4): 897-906. MRID 50531601		

A.3 Summaries of Studies Used for Endpoint Selection

Studies Selected: Weight of evidence from the chronic dog (2 studies), chronic rat (2 studies) and carcinogenicity study in the rat.

MRID Nos.: 00132394 and 00132395 (chronic toxicity studies in rats and dogs) & 00159856 (carcinogenicity in the rat, NCI study).

Executive Summaries: (adapted from the Registration Standard (Greear, TXR # 0007166, 3/23/88).

Rat studies: There are two chronic studies conducted in rats with different formulations of oxytetracycline or tetracycline (1959-1962; MRID 00132395). The *first rat study* dosed Sprague-Dawley rats, 20/sex at 0, 100 or 1000 ppm with oxytetracycline and an additional set of 20/sex were dosed with Arquad-C (a mixture of alkyl quaternary amine salts of oxytetracycline) for 24 months at 0, 1, 10, 100 or 1000 ppm. Survival was greater and there was a slight increase in body weight during the second year of the study. Hematology was similar in all groups. The testes were atrophied or degenerated with mean testes weights being lower (individual organ weights were not available). Histologically, the testes displayed degeneration arteritis or periarteritis; 0/7, 5/9, 1/9, 7/9, or 7/9 for the control, 1, 10, 100 or 1000 ppm dose groups for the Arquad treated group, and 5/10 or 4/7 for the oxytetracycline treated 100 and 1000 ppm groups, respectively.

The *second rat study* dosed only male Osborne-Mendel rats at dose levels of 0 (180 rats), 100 (100 rats), 1000 (130 rats) or 3000 ppm (100 rats) with oxytetracycline-HCl for 24 months; the same number of rats were separately dosed with tetracycline-HCl. The study was conducted to verify the apparent treatment related effect in the testes seen in the first rat study. Survival and body weight was greater in the rats dosed with the tetracyclines. There was no reported degenerative effect of treatment for either tetracycline chemical on the testes weight, gross pathology or histopathology. However, it was noted that one rat each in the 1000 and 3000 ppm dose groups had interstitial cell carcinomas (1% or less).

There is also a NCI study in rats (1986, MRID 00159856) where oxytetracycline hydrochloride was dosed as 0, 25,000 or 50,000 ppm for 103 weeks in *F344/N* rats. The peer review conclusion was that there was equivocal evidence of carcinogenicity for male F344/N rats as indicated by increased incidences of pheochromocytomas of the adrenal gland and equivocal evidence of carcinogenicity for female F344/N rats as indicated by increased incidences of

adenomas of the pituitary gland. Mean body weight tended to be lower. The adrenal medulla demonstrated hyperplasia and the liver demonstrated fatty metamorphosis and increases in accessory structures.

For the rat studies, the **NOAEL is 150 mg/kg/day** (3,000 ppm), as assigned by the Registration Standard (Greear, TXR# 0007166, 3/23/88) based on no consistent teste effects in the two rat chronic feeding studies and no similar effect seen in the NCI cancer study. The effects on the testes seen in the first study were considered to be related to aging rather than an effect of the test material. The **LOAEL is 1250 mg/kg/day** (25,000 ppm); the lowest dose in the NCI study showing liver effects. Three different strains of rat were used for each of the three rat studies.

Dog Studies: There were also two studies conducted in dogs (1959-1962; MRIDs 00132395 and 00132395). The *first dog study* consisted of only 2 dogs/sex that were dosed with diets containing 0, 2,000, 5,000 or 10,000 ppm of Arquad and an additional group dosed with the same levels of oxytetracycline for one year. The alkyl quaternary test material was not tolerated well at 5000 ppm or higher when dosed in the feed or by capsule. There were indications of testicular degeneration and disrupted spermatogenesis in one male receiving 5,000 ppm and one receiving 10,000 ppm of Arquad and in 2 males receiving 10,000 ppm of oxytetracycline.

The *second dog study* consisted of dosing 8 males (4 beagles and 4 mongrels) at 0, 100, 3000 or 10,000 ppm of oxytetracycline-HCl and an additional group dosed with tetracycline-HCl. The study was conducted to assess for an apparent effect in the testes. The dogs tolerated these preparations of oxytetracycline or tetracycline. There were no effects on either testes or epididymis weight or histopathology. Noted was an apparent increase in brown staining of the intra-cytoplasmic granules in the follicular cells of the thyroid in the dogs fed tetracycline-HCl.

For these two dog studies based on the Registration Standard (Greear, TXR# 0007166, 3/23/88), the **NOAEL is 250 mg/kg/day** (10,000 ppm), the highest dose tested.

Appendix B. International Residue Limits

(006304; 07/06/2016)

Summary of US and International Tolerances and Maximum Residue Limits				
***Residue Definition*:**				
US		**Canada**	**Mexico**	**Codex**
§ 180.337 (a) General. Oxytetracycline; (4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,6,10,12,12a-hexahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide		None		None
Commodity	***Tolerance (ppm) /Maximum Residue Limit (mg/kg)***			
	US	**Canada**	**Mexico**	**Codex**
Apple	0.35			
Peach	0.35			
Pear	0.35			
Recommended for PP# 5F8415 (D434785)				
Fruit, citrus, group 10-10	0.01			
Completed: M. Negussie; 07/07/2016				

Appendix C. Physical/Chemical Properties

TABLE B. Physicochemical Properties of Oxytetracycline Hydrochloride and Oxytetracycline Calcium		
Parameter	**Value**	**Reference**
Oxytetracycline hydrochloride (PC Code 006308)		
Melting point	Decomposes above 180 °C	RED 12/29/92
pH	2.4 (1% aqueous solution)	RED 12/29/92
Density, bulk density, or specific gravity	5.0 lbs/ft^3 1.98 g/mL (bulk density)	RD D289846, 9/9/03, S. Malak D167892, 9/22/92, F. Toghrol
Water solubility	Freely soluble in water	RD D289846, 9/9/03, S. Malak
Solvent solubility	Sparingly soluble in alcohol	RD D289846, 9/9/03, S. Malak
Vapor pressure	N/A; water soluble salt	RD D289846, 9/9/03, S. Malak
Dissociation constant, pK	N/A; water soluble salt	RD D289846, 9/9/03, S. Malak
Octanol/water partition coefficient	N/A; water soluble salt	RD D289846, 9/9/03, S. Malak
UV/visible absorption spectrum	Not available	
Oxytetracycline calcium (PC Code 006321)		
Melting point	Decomposes above 180 °C	RD D203326, 9/30/94, A. Smith
pH	8.6 (1% aqueous solution)	RED 12/29/92
Density, bulk density, or specific gravity	Bulk density: 0.39 g/cc free-flowing 0.56 g/cc compressed	RD D203326, 9/30/94, A. Smith
Water solubility	g/100 mL at 23 °C: 3.14 in pH 1.2 water 0.05 in pH 5 water 0.11 in pH 7 water 3.86 in pH 9 water	RD D203326, 9/30/94, A. Smith
Solvent solubility	Not available	
Vapor pressure	Not available	
Dissociation constant, pK_a	Not available	
Octanol/water partition coefficient	K = <10	RD D203326, 9/30/94, A. Smith
UV/visible absorption spectrum	Not available	

Appendix D. Summary of Occupational and Residential Non-Cancer Algorithms

Occupational Non-Cancer Handler Algorithms

Potential daily exposures for occupational handlers are calculated using the following formulas:

$$E = UE * AR * A * 0.001\ mg/ug$$

where:

E	=	exposure (mg ai/day),
UE	=	unit exposure (µg ai/lb ai),
AR	=	maximum application rate according to proposed label (lb ai A or lb ai/gal), and
A	=	area treated or amount handled (e.g., A/day, gal/day).

The daily doses are calculated using the following formula:

$$ADD = \frac{E * AF}{BW}$$

where:

ADD	=	average daily dose absorbed in a given scenario (mg ai/kg/day),
E	=	exposure (mg ai/day),
AF	=	absorption factor (dermal and/or inhalation), and
BW	=	body weight (kg).

Margin of Exposure: Non-cancer risk estimates for each application handler scenario are calculated using a Margin of Exposure (MOE), which is a ratio of the toxicological endpoint to the daily dose of concern. The daily dermal and inhalation dose received by occupational handlers are compared to the appropriate POD (i.e., NOAEL) to assess the risk to occupational handlers for each exposure route. All MOE values are calculated using the following formula:

$$MOE = \frac{POD}{ADD}$$

where:

MOE	=	margin of exposure: value used by HED to represent risk estimates (unitless),
POD	=	point of departure (mg/kg/day), and
ADD	=	average daily dose absorbed in a given scenario (mg ai/kg/day).

Residential Non-Cancer Handler Algorithms

Handler dermal and/or inhalation exposures are estimated by multiplying the application method-specific unit exposure by an estimate of the amount of active ingredient handled in a day, using the following algorithm:

$$E = UE * AR * A$$

where:
E = exposure (mg/day);
UE = unit exposure (mg/lb ai);
AR = application rate (e.g., lb ai/ft^2, lb ai/gal); and
A = area treated or amount handled (e.g., ft^2/day, gal/day).

Dermal and/or inhalation doses are estimated using the following algorithm:

$$D = \frac{E * AF}{BW}$$

where:
D = dose rate (mg/kg-day);
AF = absorption factor (dermal and/or inhalation); and
BW = body weight (kg).